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THE ROLE OF THE ARTERIAL CHEMORECEPTORS AND BARORECEPTORS IN THE CIRCULATORY RESPONSE TO HYPOXIA OF THE RABBIT

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The initial changes in heart rate and blood pressure observed in the conscious rabbit following inhalation of low oxygen mixtures (Korner & Edwards, 1960*a*) resemble closely the changes resulting from hypoxic stimulation of the arterial chemoreceptors in anaesthetized dogs and cats with controlled ventilation (Bernthal, Greene & Revzin, 1951; Daly & Scott, 1958, 1962, 1963*a*, *b*; Downing, Remensnyder & Mitchell, 1962; Downing & Siegel, 1963; Macleod & Scott, 1964). There has, however, been little detailed analysis in unanaesthetized animals of the reflex mechanisms underlying the changes in heart rate, cardiac output and blood pressure during different types of systemic hypoxia. The present report considers the role of the arterial chemoreceptors and baroreceptors in hypoxia resulting from the inhalation of low oxygen mixtures and small concentrations of carbon monoxide in air. The former gas mixture leads to a fall in both the arterial and tissue P_{O_2}, but with carbon monoxide the arterial P_{O_2} remains normal although tissue hypoxia is produced (Haldane & Priestley, 1935; Asmussen & Chiodi, 1941; Korner, 1959). Inhalation of carbon-monoxide mixtures is not, therefore, associated with increased activity of the arterial chemoreceptors (Duke, Green & Neil, 1952; Joels & Neil, 1961). Assessment of the effects of chemoreceptor reflexes has been made by contrasting the circulatory effects of low O_2 mixtures with those of CO in the normal animal with intact reflexogenic zones, and also with the effects of low O_2 in 'denervated' animals following chronic section of the carotid and aortic nerves.

Since inhalation of carbon monoxide does not result in excitation of arterial chemoreceptors, a comparison of the circulatory effects of this gas in the normal rabbit with the effects observed in 'denervated' animals permits assessment of the part played by the arterial baroreceptors in this type of systemic hypoxia.

METHODS

Animals. New Zealand White rabbits, cross-bred with New Zealand Giant Strain, varying in weight from 2·0 to 3·6 kg, were used for these experiments.

Operative procedures and conduct of experiments

At a preliminary operation under sodium pentobarbitone anaesthesia (Veterinary Nembutal, Abbott; initial dose 30–40 mg/kg I.V. supplemented as required) carried out using aseptic procedures 3–8 days before each experiment, a thermistor catheter was inserted into the upper part of the abdominal aorta via the ilio-lumbar artery, as described previously (Korner, 1965). The trachea was placed into a more subcutaneous position by suturing the pre-tracheal muscles loosely behind it (Edwards, Korner & Thorburn, 1959). In a second group of rabbits bilateral section of the carotid and aortic nerves was carried out under pentobarbitone anaesthesia (Korner, 1965). The incisions were closed, and the animals given 50 mg terramycin intramuscularly. The animals in both groups recovered rapidly from the effects of the operation. Only animals which regained normal activity, and were eating and drinking, were used for subsequent experiments.

On the day of the experiment, 3–8 days following the preliminary operation, all operative procedures were carried out under local anaesthesia, comprising infiltration of the skin and subcutaneous tissues of the ear and neck, with ½% lignocaine HCl (Xylocaine). Fine polyvinylchloride (PVC) catheters were inserted into the central ear artery and right atrium (through the external jugular vein) and a light metal tracheotomy tube was introduced into the trachea as described previously (Edwards *et al.* 1959). The incisions were closed following further infiltration of the skin edges with local anaesthetic, and the rabbit was placed without restraint inside a large rabbit box, where it sat comfortably throughout the experiment without any signs of distress. All measurements and sampling procedures were carried out without touching the animal, using long leads and catheters. The noise level in the laboratory was low, and the temperature was maintained at $22 \pm 1°$ C.

The experiment commenced 1 hr after first placing the animal inside the rabbit box, and consisted of a control period (breathing room air), a test period (breathing the test gas mixture), and a recovery period (breathing room air) (Fig. 1). Measurements of cardiac output, heart rate, arterial pressure, right atrial pressure, ventilation and aortic blood temperature were carried out at frequent intervals as shown in Fig. 1. One arterial blood sample was obtained during the control period, and a second sample was obtained after 35 min exposure to the test mixture. This initial experiment was followed in all cases by a second experiment, in which the effects of another test gas were examined in the same animal, in view of the advantages of such within-animal comparisons for quantitative assessment of the effects of different treatments. The order in which any two test mixtures were administered was alternated, to avoid any systematic interaction of residual treatment effects.

In five rabbits tracheotomy was not carried out, but the circulatory response to inhalation of low O_2 mixtures was examined on two occasions before and after carotid denervation or sham operation.

Measurement of cardiac output, blood pressure and heart rate

Cardiac output was measured by the thermodilution method (Fegler, 1954). Rapid changes in aortic-blood temperature were recorded by means of a fast responding thermistor following injection of 0·4–0·6 ml. of 0·9% NaCl at room temperature into the right atrium (Korner, 1965).

Arterial and right atrial pressures were recorded using a Statham P23D strain gauge and a Sanborn carrier preamplifier, and mean pressures were obtained by electronic damping.

Arterial pressure was measured from the central ear artery while recording each thermodilution curve (Fig. 2), and the heart rate was obtained from the pressure record. Total peripheral resistance was calculated as the ratio of mean ear-artery pressure (mm Hg)/cardiac output (ml./min) and expressed in arbitrary units (P.R.U.). Right atrial pressure was determined immediately after each measurement of cardiac output, through the injection catheter. The catheter position in the atrium was confirmed at autopsy at the end of each experiment. The zero reference plane for arterial and right atrial pressure measurement was an arbitrary plane 3 cm above the floor of the rabbit box, which corresponded approximately to a plane passing through the top of the sternum when the animal assumed its usual posture in the box.

Administration of gas mixtures. Gas mixtures, freshly prepared before use from cylinders of air, N_2, CO_2 and 0·5 % CO in 21 % O_2, were administered to the animals from a light polythene bag through the respiratory valve assembly described by Edwards *et al.* (1959) and Korner (1963). Expired air was collected in a small rubber bag for period of 30–60 sec following measurement of cardiac output, and the volume measured with a wet gas metre. In view of the changes in body temperature observed in many of the experiments the ventilation has been expressed as ml/min of dry gas at s.t.p. In five experiments animals in which tracheotomy had not been carried out received gas mixtures inside an air-tight Perspex box of 14 l. capacity, by drawing the gas through the box at the rate of 8 l./min, with a water suction pump.

Blood gas and pH measurements. Arterial blood was collected anaerobically (Edwards *et al.* 1959) using 2·5 ml. of blood for each set of analyses. O_2 and CO_2 content were determined from 0·5 ml. samples by the manometric method of Van Slyke & Neill (1924). The O_2 capacity was determined from the haemoglobin concentration, using the cyanmethaemoglobin method of Drabkin & Austin (1935). The optical density was measured at a wavelength of 540 mμ on a Beckman Model DU spectrophotometer. pH measurements were carried out on whole blood immediately after collection, at the rabbit's average body temperature of 40° C (Stokes & Korner, 1964), and were corrected to the animal's actual aortic blood temperature by means of the factors of Rosenthal (1948). pH was measured to an accuracy of $\pm$ 0·005 units, using an E.I.L. Model C33B Vibron Electrometer pH meter with a flow-type glass-electrode system (Electronic Instruments, Ltd, Richmond, Surrey). Arterial P_{CO_2} was calculated from the Henderson–Hasselbalch equation from the total blood CO_2 concentration, arterial pH, haemoglobin concentration, arterial oxyhaemoglobin saturation and aortic blood temperature, using the solubility factor 'S', and the pK′ values determined by Severinghaus, Stupfel & Bradley (1956*a*, *b*). Examination of the CO_2 dissociation curve for rabbit blood (Korner & Darian-Smith, 1954) suggests that these factors apply also to rabbit blood. Serum CO_2 concentration (mM) was calculated from total blood CO_2 using the factor 'f' of Van Slyke & Sendroy (1928). Approximate arterial P_{O_2} was calculated from the arterial saturation, using the rabbit's oxyhaemoglobin dissociation curve (Korner & Darian Smith, 1954) and standard temperature and pH corrections (Severinghaus, 1958).

Statistical methods. When analysing the average response pattern in a group of animals from the results of individual experiments (e.g. Fig. 1), the means of each variable have been calculated for the selected time intervals shown, with 2–4 measurements of each variable from each animal contributing to each time interval. The standard error of the mean of each variable for each time interval has been estimated by analysis of variance (Mather, 1949; Cochran & Cox, 1953) from the error mean square, after removing 'between animals' and 'between times' sums of squares from the total sum of squares. It was calculated from the formula S.E. of mean = $\sqrt{}$(error mean square/n) where n = number of animals in the group. The results are given in the legends to the relevant illustrations (Figs. 3, 5–8) describing the various response patterns.

RESULTS

Stability of preparation in control experiments

In each of six control experiments in which the animals inhaled 21 % O_2 during the test period, the ventilation and arterial pressure varied but little, but larger, slow fluctuations in cardiac output (S.D. ± 7 % of mean value) were evident (Fig. 1, left panel). These slow fluctuations were not

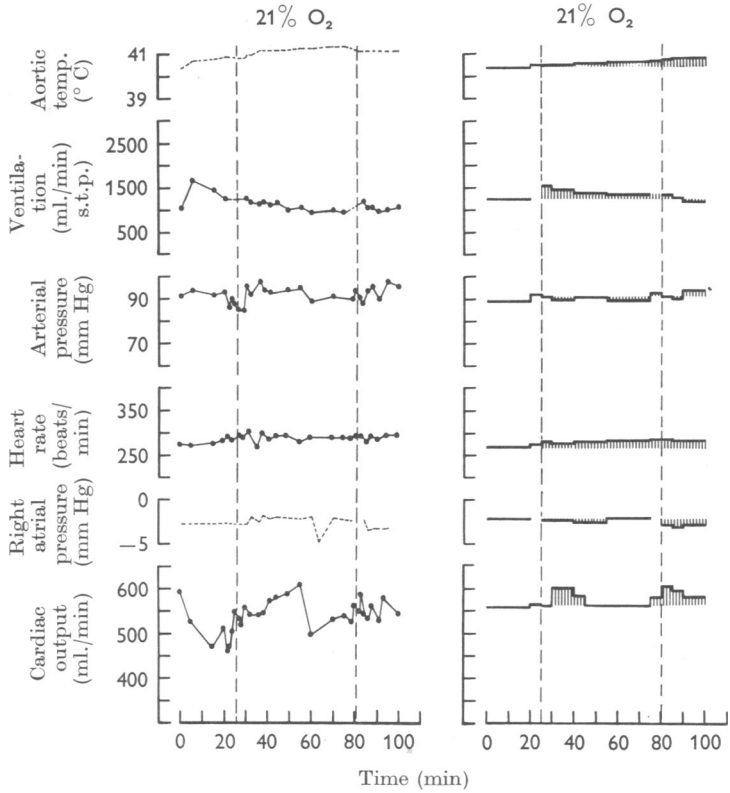

Fig. 1. *Left.* Results of control experiment in normal rabbit, which breathed 21 % O_2 from air cylinder through a bag-valve assembly (between vertical interrupted lines) and room air through a valve at other times. Arterial blood was taken at 5 min (control) and 60 min (test sample). *Right.* Mean values from six rabbits grouped in the time intervals shown; the standard error of the mean (S.E.) of each variable was calculated by analysis of variance (see Methods) and is given in brackets after each variable below. Deviations of each variable from initial control values represented by vertical hatching. In all figures a significant change from initial control values is marked by one asterisk if $P < 0{\cdot}05$, and by two asterisks if $P < 0{\cdot}01$. Effect of inhalation of 21 % O_2 (between vertical interrupted lines) on aortic blood temperature **(S.E. = 0·08)° C; ventilation at s.t.p. (S.E. = 98) ml./min; ear artery pressure (S.E. = 3·2) mm Hg; heart rate **(S.E. = 4·4) beats/min; right atrial pressure (S.E. = 0·29) mm Hg; cardiac output *(S.E. = 15·7) ml./min, fourth and seventh time interval only.

related to any particular period of the experiment. Owing to their random occurrence these cardiac output oscillations were not apparent when calculating the mean response pattern of the whole group (Fig. 1, right panel). However, a small, transient, but statistically significant ($P = 0{\cdot}01$) increase of about 5 % of the mean cardiac output value was invariably superimposed on the slow oscillations in cardiac output at the beginning and end of each test period, coinciding with the period of more frequent measurement. The mechanism of the effect has not been investigated but it must be considered when assessing the effects of the various treatments on cardiac output. The heart rate showed a slight but significant upward trend averaging $12 \pm 4{\cdot}4$ (S.E. of mean) beats/min.

TABLE 1. Changes in arterial blood composition during various test procedures in different groups of normal and 'denervated' rabbits

No.	Test gas	Arterial P_{CO_2} (mm Hg)		Arterial pH		Arterial saturation* (%)	
		C	*T* S.E.Δ	*C*	T S.E.Δ	*C*	*T* S.E.Δ
			Normal rabbits				
6	21 % O_2	30	29 ±4·0	7·46	7·46 ±0·053	95	95 ±1·2
2	21 % O_2 + 5 % CO_2	27	44 ±2·5	7·43	7·36 ±0·02	95	100 ±0·5
4	8 % O_2	28	10 ±1·8	7·52	7·60 ±0·054	96	59 ±8·1
8	9 % O_2	28	14 ±2·1	7·79	7·68 ±0·025	95	76 ±6·0
3	9 % O_2 + 5 % CO_2	24	47 ±6·6	7·51	7·26 ±0·068	96	67 ±5·8
6	0·2 % CO	25	21 ±0·7	7·49	7·46 ±0·023	95	49 ±2·4
3	0·2 % CO + 21 % O_2 + 5 % CO_2	31	48 ±5·0	7·47	7·36 ±0·050	94	42 ±2·7
4	0·1 % CO	27	22 ±1·9	7·48	7·53 ±0·037	95	65 ±3·7
			'Denervated' rabbits				
1	21 % O_2	27	29 —	7·49	7·47 —	93	92 —
2	21 % O_2 + 5 % CO_2	30	41 ±1·0	7·47	7·41 ±0·02	92	97 ±1·0
5	10·5 % O_2	34	26 ±3·0	7·46	7·47 ±0·082	93	48 ±3·5
4	11·5 % O_2	24	17 ±2·1	7·56	7·60 ±0·023	95	74 ±2·7
4	9 % O_2 + 5 % CO_2	27	40 ±6·2	7·48	7·55 ±0·082	98	61 ±6·6
3	0·2 % CO	27	22 ±2·2	7·55	7·48 ±0·055	98	54 ±3·2
3	0·1 % CO	25	25 ±2·5	7·56	7·52 ±0·037	96	63 ±4·5

C = control values breathing room air.

T = test values.

S.E.Δ = S.E. of difference calculated as within animal comparisons.

* In animals breathing CO mixtures saturation = $(HbO_2)/(HbO_2 + HbCO + Hb)$.

Effects of hypoxia and hypercapnia in normal rabbits

Effects of inhalation of low O_2 mixtures. The present experiments extend previous work on the effects of hypoxia on the cardiac output of the rabbit (Korner & Edwards, 1960*a*, *b*), since the thermodilution method allows more frequent measurement of cardiac output than was possible with Fick and dye-dilution methods, thus permitting a better description of the time course of the circulatory response to hypoxia.

Inhalation of 8 % O_2 produced marked reduction in arterial P_{O_2} from

its normal level to 30 mm Hg (range 24–33 mm Hg), and P_{CO_2} from its normal value of 28 mm Hg to 10 mm Hg (range 7–15 mm Hg) (Table 1). During the initial phase of hypoxia marked bradycardia, reduction in cardiac output and a small rise in blood pressure were observed in all four animals (Figs. 2 and 3). With continuing hypoxia the cardiac output returned rapidly to control values but a lesser degree of bradycardia persisted (Figs. 2 and 3; Table 2). The calculated peripheral resistance was

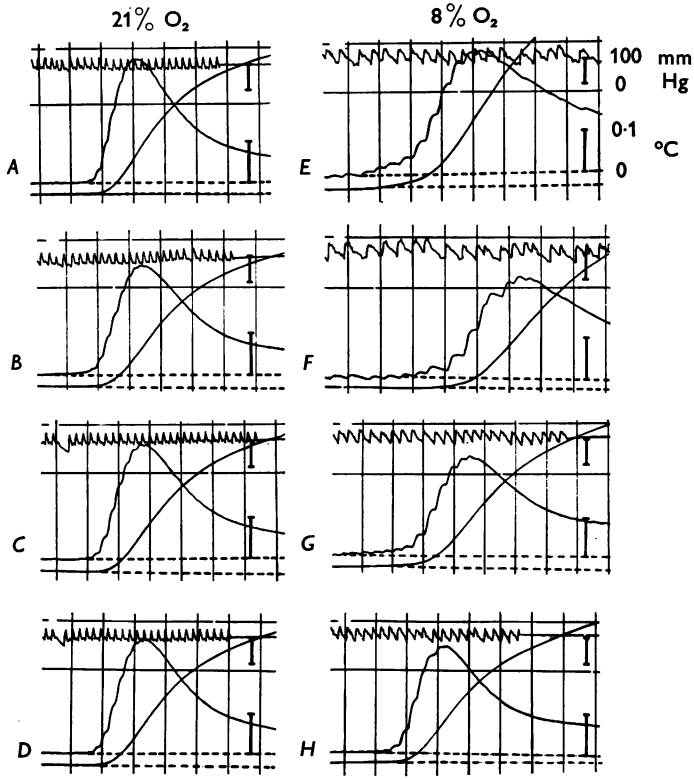

Fig. 2. Effect of inhalation of 8 % O_2 on cardiac output, ear-artery pressure and heart rate in a normal rabbit. Each record from above downwards: signal marker, ear-artery pressure, thermodilution curve, area of thermodilution curve; time intervals, 1 sec. At break in signal, 0·5 ml. of 0·9 % NaCl at room temperature rapidly injected into right atrium. Records on left from above *A–D* are control records (room air) 10, 4, 2, and 1 min before changing inspired gas to 8 % O_2 at top right; then from above *E–H* downwards after 1, 2, 4 and 10 min hypoxia.

significantly increased throughout the period of treatment, but reached a maximum during the initial phase of hypoxia (Table 2). During the period of recovery the blood pressure rapidly returned to initial control values, and this was associated with significant tachycardia, reduction in right atrial pressure and cardiac output (Fig. 3).

Although there was only slightly less severe reduction in arterial P_{O_2} and P_{CO_2} following inhalation of 9% O_2 than after breathing 8% O_2 (Table 1), the circulatory findings differed considerably (Fig. 3). After an initially variable response in different animals, the heart rate increased steadily during inhalation of 9% O_2, exceeding initial control values in

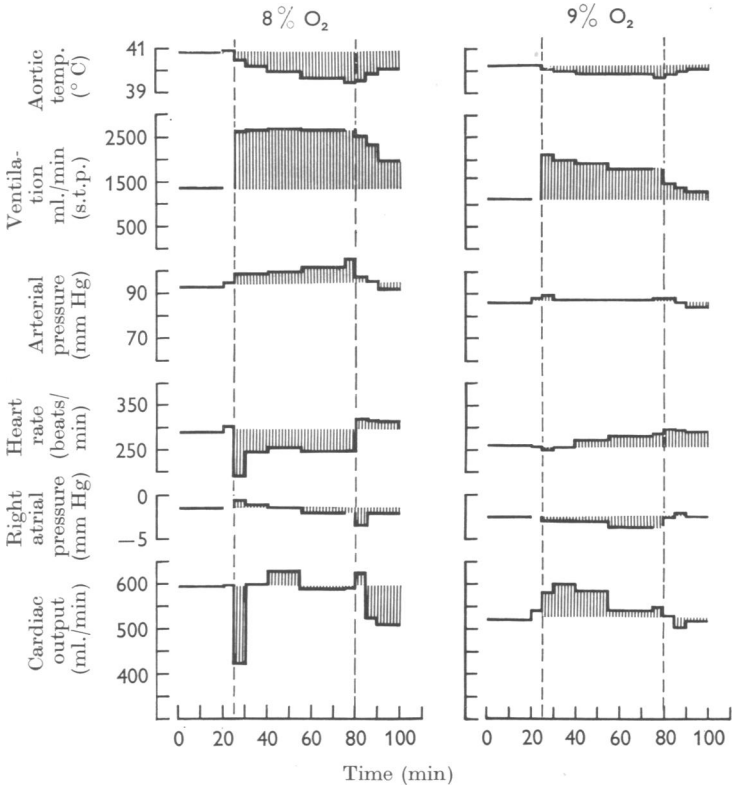

Fig. 3. *Left.* Mean effect in four normal rabbits of inhalation of 8% O_2 on aortic blood temperature **(S.E. = 0·19° C; ventilation at s.t.p. **(S.E. = 141) ml./min; ear-artery pressure **(S.E. = 2·4) mm Hg; heart rate **(S.E. = 11·4); right atrial pressure (S.E. = 0·62); cardiac output *(S.E. = 28·0) ml./min. *Right.* Mean effect in eight normal rabbits of inhalation of 9% O_2 on aortic blood temperature **(S.E. = 0·08)° C; ventilation at s.t.p. **(S.E. = 85) ml./min; ear-artery pressure (S.E. = 2·2) mm Hg; heart rate **(S.E. = 6·4); right atrial pressure (S.E. = 0·13); cardiac output **(S.E. = 12·6) ml./min.

seven of eight animals, with an average maximum increase of $34 \pm 7{\cdot}1$ (S.E. of mean) beats/min. The cardiac output reached a maximum value of $117 \pm 1{\cdot}4$ (S.E. of mean) % of control during the first 10 min of hypoxia, and remained significantly elevated during the first 30 min of the test period (Fig. 3), coinciding with the period of maximum increase in ventilation. The change in cardiac output at this time exceeded that observed in

control experiments (Fig. 1) and is thus considered to be significant. Since there was no significant change in arterial pressure at this time the calculated TPR decreased.

The aortic blood temperature fell markedly with both mixtures during the test period, with greater and more rapid reduction during exposure to 8 % O_2.

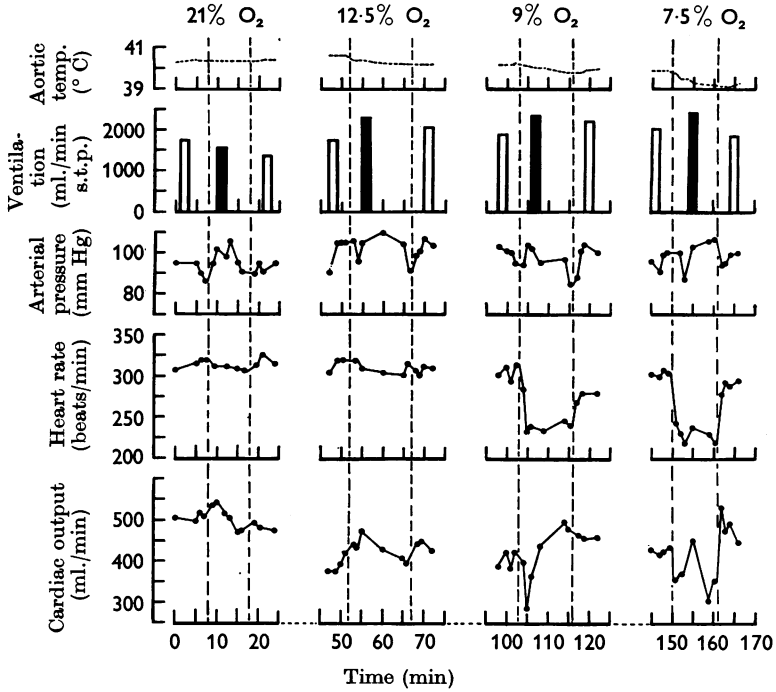

Fig. 4. Effects in normal rabbit of breathing 21 % O_2, 12·6 % O_2, 9 % O_2 and 7·5 % O_2, with animal inhaling mixtures (between vertical interrupted lines) and room air at other times. Estimated arterial P_{O_2} was 95, 50, 33 and 26 mm Hg in the four successive test periods.

The circulatory effects of graded degrees of reduction in arterial P_{O_2} were investigated in four rabbits. Figure 4 illustrates one of these experiments, in which the animal's respiratory response to the various low O_2 mixtures was somewhat inadequate, so that owing to the relatively constant increase in ventilation with each mixture progressive lowering in arterial P_{O_2} resulted. When the latter was reduced to 50 mm Hg (12·6 % O_2 in Fig. 4) no significant circulatory effects were observed. Reducing the arterial P_{O_2} to 33 mm Hg (9 % O_2 in Fig. 4) resulted in persistent bradycardia with only transient reduction in cardiac output. Further reduction of the P_{O_2} to 26 mm Hg (7·5 % O_2 in Fig. 4) resulted in more marked bradycardia and persistent reduction in cardiac output. This experiment

also demonstrates that the degree of reduction in aortic blood temperature is related to the severity of arterial hypoxia and does not merely reflect the degree of hyperventilation.

Effects of inhalation of CO mixtures. The arterial O_2 content was reduced during inhalation of 0·1 % CO + 21 % O_2 (0·1 % CO), and of 0·2 % CO + 21 % O_2 (0·2 % CO), owing to the formation of carboxyhaemoglobin, and there

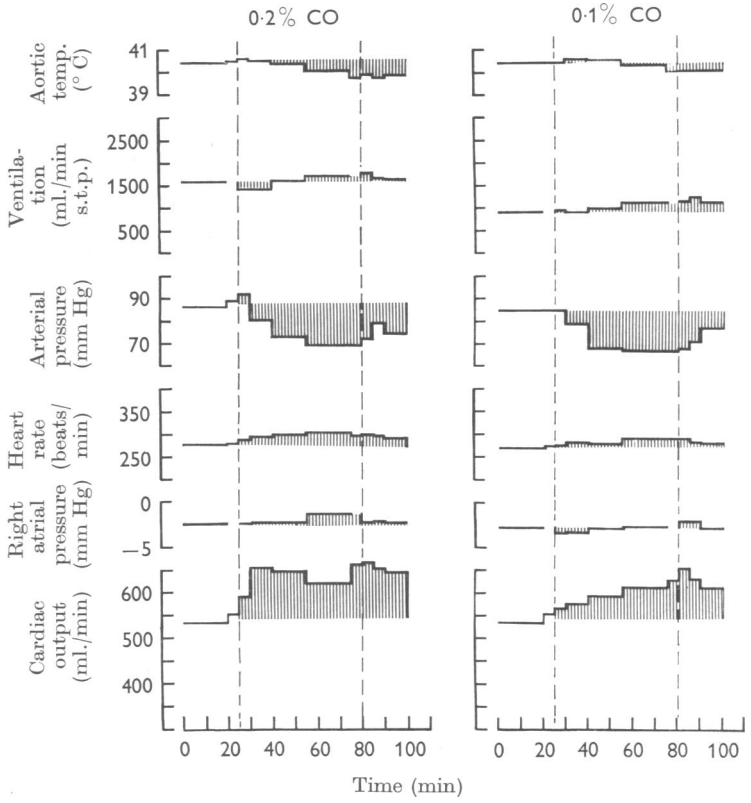

Fig. 5. *Left.* Mean effect in five normal rabbits of inhalation of 0·2 % CO on aortic blood temperature **(S.E. = 0·15)° C; ventilation at s.t.p. (S.E. = 107) ml./min; ear-artery pressure **(S.E. = 3·1) mm Hg; heart rate *(S.E. = 11·1) beats/min; right atrial pressure (S.E. = 0·26) mm Hg; cardiac output **(S.E. = 26·4) ml./min. *Right.* Mean effect in four normal rabbits of inhalation of 0·1 % CO on aortic blood temperature (S.E. = 0·12)° C; ventilation at s.t.p. (S.E. = 111) ml./min; ear-artery pressure *(S.E. = 4·6) mm Hg; heart rate (S.E. = 7·8; P = 0·07) beats/min; right atrial pressure (S.E. = 0·56) mm Hg; cardiac output *(S.E. = 16·8) ml./min.

was slight reduction in arterial P_{CO_2} (Table 1). Changes in ventilation were small (Fig. 5), in agreement with the hypothesis of normal arterial chemoreceptor activity in this type of hypoxia (Duke *et al.* 1952; Joels & Neil, 1961).

Inhalation of 0·2 % CO resulted in elevation of cardiac output, reduction in arterial pressure and TPR, and slight tachycardia. The increase in heart rate averaged 26 beats/min, being thus twice as great as that observed in control experiments (Fig. 1). There was a small but significant elevation in right atrial pressure in the latter part of the test period (Fig. 5). With 0·1 % CO the changes in cardiac output were smaller and of slower onset than during exposure to 0·2 % CO, but the changes in blood pressure were similar with both mixtures. The increase in heart rate was similar to that seen in control experiments, and does not therefore probably represent a physiological effect of CO (Fig. 5).

Recovery from the circulatory effects of CO mixtures was slow in all animals (Fig. 5). In five rabbits studied for longer during the recovery phase (three after breathing 0·2 % CO; two after breathing 0·1 % CO) the cardiac output had risen to $115 \pm 4{\cdot}5$ (S.E. of mean) % of control during the test period, increasing slightly to $122 \pm 4{\cdot}3$ (S.E. of mean) % of control during the first 20 min recovery. Recovery was only half complete 1 hr later, being $110 \pm 3{\cdot}1$ (S.E. of mean) % of control, although the arterial COHb concentration was only 0·5 ml./100 ml. of blood (range 0·4–0·6 ml./100 ml.). Probably the prolonged action of CO is the result of some extravascular binding (e.g. by myoglobin) (Hill, 1936). Removal of CO from such sites would be slow, and possibly some local interference with tissue respiration may be related to the prolonged circulatory effects. No such residual effects were observed following inhalation of low O_2 mixtures, but the prolonged action of CO mixtures appeared to be without effect on the animal's subsequent response to the inhalation of low O_2 mixtures.

The rate of fall in aortic-blood temperature was smaller after inhalation of CO mixtures, than after exposure to low O_2 mixtures.

Quantitative comparisons within animals of effects of breathing low O_2 and CO mixtures. The effects produced by breathing 8 % O_2 were contrasted with those of 0·2 % CO in each of four rabbits, whilst in four others the effects of 9 % O_2 were compared with those of 0·1 % CO. The reduction in mixed venous P_{O_2} is approximately similar with each set of comparisons (Korner, 1963). The differences in the effect produced in each set of comparisons will thus mainly reflect differences in arterial P_{O_2} (and P_{CO_2}).

During the first 5 min of hypoxia the circulatory effects of inhaling 0·2 % CO were small, in contrast to the marked bradycardia, reduction in cardiac output and increased TPR observed with 8 % O_2 (Table 2). During 'steady state' conditions during the last 30 min of the test period some bradycardia and elevation in TPR were still present with 8 % O_2, whilst exposure to 0·2 % CO resulted in an increase in cardiac output and heart rate above initial control values and a fall in TPR (Table 2).

Differences in the circulatory effects of inhalation of 9 % O_2 and 0·1 %

CO during the first 5 min of hypoxia were small. Subsequently the maximum increase in cardiac output occurred at different times with the two types of hypoxia (Figs. 3 and 5). The maximum increase in heart rate was always greater during inhalation of 9 % O_2 ($+42 \pm 7{\cdot}8$ (S.E. of mean) beats/min), than when breathing 0·1 % CO ($+16 \pm 3{\cdot}8$ (S.E. of mean) beats/min). Average differences in the circulatory variables are summarized in Table 2.

TABLE 2. Comparison of effects in the same animals of breathing 8 % O_2 and 0·2 % CO or 9 % O_2 and 0·1 % CO. The mean initial response (*I.R.*) during the first 5 min of breathing the test mixture, and the mean steady-state (*S.S.*) response during the last 30 min of the test are expressed as a percentage of the animals initial control values. S.E. of mean effect is given with each variable. An asterisk denotes a significant change from initial control ($P < 0{\cdot}05$)

			% of control			
No.	Test mixture	Period	Cardiac output	Heart rate	Blood pressure	TPR
4	8 % O_2	*I.R.*	$72 \pm 8{\cdot}2$*	$63 \pm 5{\cdot}3$*	$105 \pm 3{\cdot}5$	$145 \pm 13{\cdot}1$*
		S.S.	$100 \pm 2{\cdot}2$	$85 \pm 4{\cdot}3$*	$110 \pm 3{\cdot}0$*	$110 \pm 3{\cdot}2$*
	0·2 % CO	*I.R.*	$113 \pm 2{\cdot}8$*	$103 \pm 3{\cdot}1$	$105 \pm 3{\cdot}9$	$94 \pm 5{\cdot}3$
		S.S.	$118 \pm 4{\cdot}4$*	$110 \pm 3{\cdot}2$*	$85 \pm 1{\cdot}6$*	$73 \pm 1{\cdot}8$*
4	9 % O_2	*I.R.*	$104 \pm 3{\cdot}3$	$96 \pm 3{\cdot}1$	$101 \pm 3{\cdot}7$	$97 \pm 4{\cdot}6$
		S.S.	$100 \pm 9{\cdot}6$	$117 \pm 5{\cdot}0$*	$105 \pm 5{\cdot}8$	$108 \pm 12{\cdot}8$
	0·1 % CO	*I.R.*	$104 \pm 1{\cdot}7$	$100 \pm 5{\cdot}9$	$99 \pm 1{\cdot}6$	$95 \pm 2{\cdot}8$
		S.S.	$114 \pm 3{\cdot}6$*	$106 \pm 2{\cdot}0$*	$79 \pm 5{\cdot}7$*	$70 \pm 5{\cdot}7$*

Interaction of effects of hypercapnia with those of low O_2 and of carbon monoxide. The differences in circulatory findings following inhalation of low O_2 and CO mixtures need not necessarily result from differences in arterial P_{O_2}, since there were also differences in P_{CO_2}, pH and in respiratory activity (Table 1; Figs. 3 and 5). The relative importance of the above factors was assessed in an experiment in which 5 % CO_2 was added to each of the following inspired mixtures: 21 % O_2; 9 % O_2; 0·2 % CO + 21 % O_2. The results in Table 1 show that the arterial P_{CO_2} was elevated to an approximately similar degree with all three mixtures, whilst the pH was similarly reduced. The arterial blood in the three groups of animals thus differed mainly with respect to P_{O_2}. Some hyperventilation was present with all three mixtures, though this was maximal in animals breathing 9 % O_2 + 5 % CO_2 (Fig. 6).

There was slight, transient bradycardia following exposure to 21 % O_2 + 5% CO_2, in agreement with previous findings (Korner & Edwards, 1950*c*), but no significant change in blood pressure or cardiac output (Fig. 6). The increase in ventilation was similar to that observed in animals breathing 0·2 % CO + 21 % O_2 + 5 % CO_2, suggesting absence of respiratory depression by CO. The normal effects of CO on the circulation did not appear to be modified by the occurrence of hyperventilation (cf. Figs. 5 and 6).

The arterial P_{O_2} was not reduced as much when breathing 9 % O_2 + 5 % CO_2, as during inhalation of 9 % O_2 alone (Table 1) owing to the greater degree of hyperventilation (cf. Figs. 3 and 6). The circulatory changes consisted of persistent bradycardia, reduction in cardiac output and increased TPR, resembling the effects of *more* severe reduction in arterial P_{O_2}, such as observed during inhalation of 8 % O_2 (cf. Figs. 3 and 6).

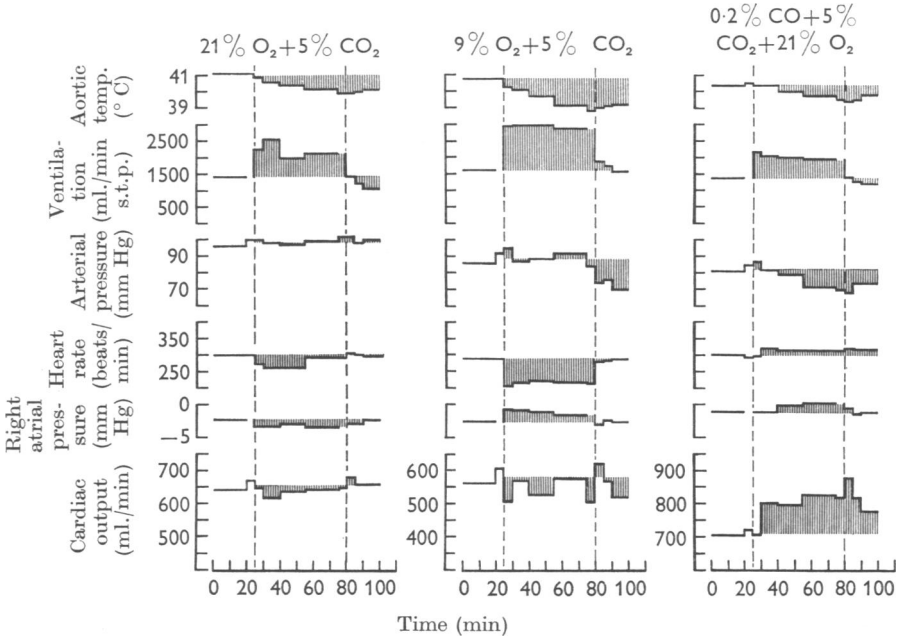

Fig. 6. *Left.* Mean effects in two normal rabbits of inhalation of 21 % O_2 + 5 % CO_2 on aortic blood temperature **(S.E. = 0·30)° C; ventilation at s.t.p. **(S.E. = 100) ml./min; ear-artery pressure (S.E. = 1·5) mm Hg; heart rate (S.E. = 10) beats/min; right atrial pressure (S.E. = 0·75) mm Hg; cardiac output (S.E. = 32) ml./min. *Middle.* Mean effect in three normal rabbits of inhalation of 9 % O_2 + 5 % CO_2 on aortic blood temperature **(S.E. = 0·37)° C; ventilation at s.t.p. **(S.E. = 160) ml./min; ear-artery pressure (S.E. = 4·0) mm Hg; heart rate **(S.E. = 12) beats/min; right atrial presssure *(S.E. = 0·40) mm Hg; cardiac output **(S.E. = 19) ml./min. *Right.* Mean effect in three normal rabbits of inhalation of 0·2 % CO + 21 % O_2 + 5 % CO_2 on aortic blood temperature **(S.E. = 0·18)° C; ventilation at s.t.p. **(S.E. = 87) ml./min; ear-artery pressure **(S.E. = 2·9) mm Hg; heart rate *(S.E. = 5·5) beats/min; right atrial pressure (S.E. = 0·60) mm Hg; cardiac output **(S.E. = 32) ml./min.

The results suggest that the main differences in the circulatory effects of low O_2 and of CO mixtures depend on differences in arterial P_{O_2}, rather than in P_{CO_2} and pH. Hypercapnia potentiates the circulatory effects of reduced arterial P_{O_2}, but not those of CO.

Effects of hypoxia and hypercapnia in rabbits with chronic section of carotid and aortic nerves

Effects of inhalation of low O_2 mixtures. Following chronic section of the carotid and aortic nerves administration of 10·5 % O_2 had no effect on ventilation (Fig. 7), indicating that denervation was complete. The arterial

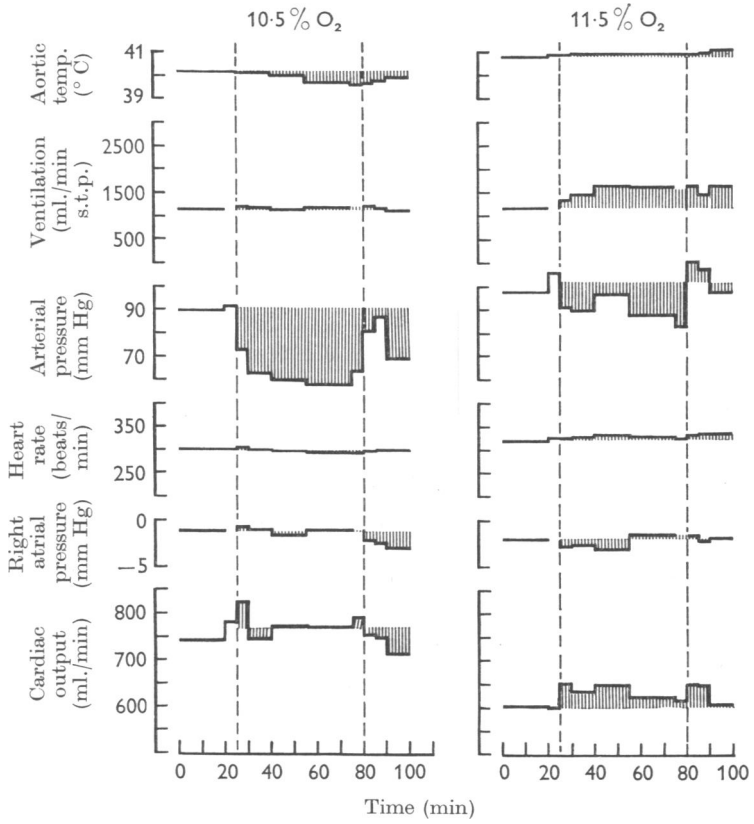

Fig. 7. *Left.* Mean effect in five 'denervated' rabbits of inhalation of 10·5 % O_2 on aortic blood temperature (S.E. = 0·13)° C; ventilation at s.t.p. (S.E. = 79) ml./min; ear-artery pressure **(S.E. = 4·6) mm Hg; heart rate (S.E. = 5·9); right atrial pressure (S.E. = 0·39) mm Hg; cardiac output (S.E. = 28·6) ml./min. *Right.* Mean effect in four 'denervated' animals of inhalation of 11·5 % O_2 on aortic blood temperature (S.E. = 0·10)° C; ventilation at s.t.p. **(S.E. = 111) ml./min; ear-artery pressure *(S.E. = 6·4) mm Hg; heart rate (S.E. = 4·0) beats/min; right atrial pressure (S.E. = 0·61) mm Hg; cardiac output (S.E. = 39·0) ml./min.

P_{O_2} was reduced to a mean value of 27 mm Hg (range 23–30 mm Hg) in these animals, slightly below the value found in rabbits with intact reflexogenic zones breathing 8 % O_2. Owing to the absence of ventilatory response

reduction in P_{CO_2} was smaller in 'denervated' than in normal rabbits (Table 1).

The circulatory changes following inhalation of 10·5 % O_2 consisted of an abrupt large fall in arterial pressure (Fig. 7) but the cardiac output was maintained at its elevated value (Korner, 1964), and the right atrial pressure did not change. Changes in heart rate were small and variable. During the early part of the recovery period the blood pressure returned rapidly to normal (Fig. 7), suggesting a rapid increase in vascular resistance coinciding with the period of rapid re-oxygenation of the arterial blood. This was followed by a further fall in arterial pressure associated with significant reduction in right atrial pressure, cardiac output and TPR possibly resulting from persistent local circulatory effects of tissue metabolites. Further observations 1 hr later in three of the above animals showed complete recovery to initial control values.

Inhalation of 11·5 % O_2 resulted in reduction in arterial P_{O_2} to 37 mm Hg (range 33–45) thus equalling the effect of 9 % O_2 in normal animals, and slight reduction in P_{CO_2} (Table 1). With 11·5 % O_2 the ventilation increased gradually after 5–10 min hypoxia in all four animals tested (Fig. 7), reaching a value of $141 \pm 9{\cdot}2$ (S.E. of mean) % of control. The possibility that chemoreceptor denervation was incomplete in these animals is unlikely since no increase in ventilation was observed in the three animals tested with 10·5 % O_2 at the end of the experiment. Similarly findings of (?) central respiratory excitation have been made in dogs with chronic denervation of the chemoreceptors (Davenport, Brewer, Chambers & Goldschmidt, 1947). Circulatory changes observed during inhalation of 11·5 % O_2 were similar to those seen with 10·5 % O_2, but were smaller in magnitude (Fig. 7). During the rapid re-oxygenation phase in the early part of the recovery period the blood pressure rose transiently above initial control values, suggestive of transient vasoconstriction.

The aortic blood temperature did not change in 'denervated' animals breathing 11·5 % O_2, and fell to a much smaller degree during inhalation of 10·5 % O_2 than in normal rabbits subjected to a similar reduction in arterial P_{O_2}.

In three rabbits the effects of reducing the arterial P_{O_2} to approximately 30 mm Hg were studied before and after nerve section, and the circulatory responses were also examined on two occasions in two sham-operated rabbits. In the latter the previous operation did not modify the effects of low O_2 mixtures demonstrating that the changes in response observed in the 'denervated' animals were specifically the result of section of the carotid sinus and aortic nerves.

Effects of inhalation of CO mixtures. The changes in arterial blood gas composition were similar in normal and 'denervated' rabbits during in-

halation of 0·1–0·2 % CO (Table 1) and there was no significant change in respiratory minute volume in either group (Fig. 8).

Inhalation of 0·2 % CO resulted in a marked abrupt fall in arterial pressure and a small but significant ($P < 0·05$) increase in right atrial pressure and cardiac output. The fall in blood pressure was greater than in

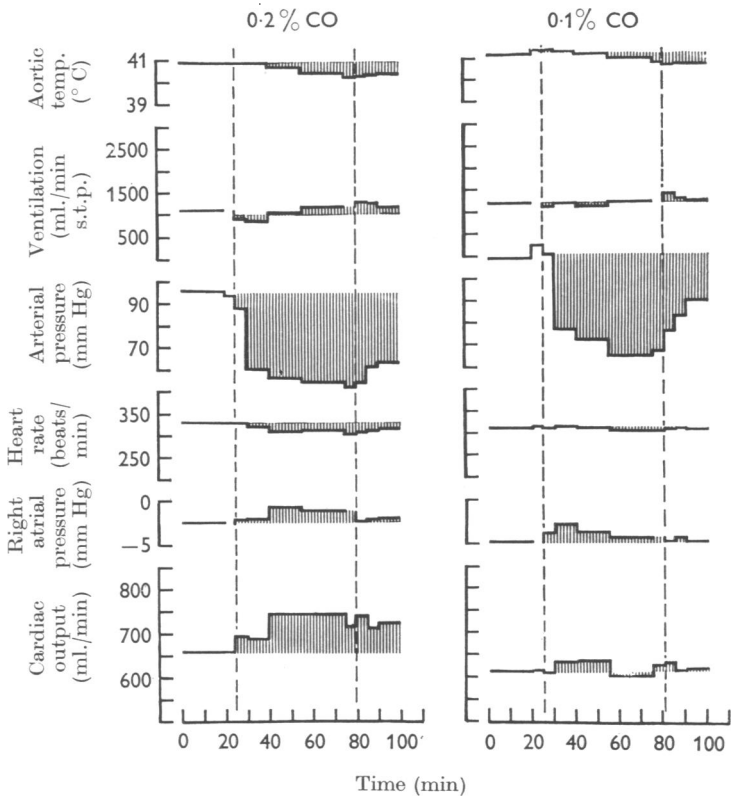

Fig. 8. *Left.* Mean effect in three 'denervated' rabbits of inhalation of 0·2 % CO on aortic temperature (S.E. = 0·10)° C; ventilation at s.t.p. (S.E. = 74) ml./min; ear-artery pressure **(S.E. = 4·3) mm Hg; heart rate **(S.E. = 6·4) beats/min; right atrial pressure *(S.E. = 0·40) mm Hg; cardiac output *(S.E. = 24) ml./min. *Right.* Mean effect in three 'denervated' rabbits of inhalation of 0·1 % CO on aortic temperature (S.E. = 0·11)° C; ventilation at s.t.p. (S.E. = 140) ml./min; ear-artery pressure **(S.E. = 8·1) mm Hg; hear rate (S.E. = 8·0) beats/min; right atrial pressure (S.E. = 0·90) mm Hg; cardiac output (S.E. = 52·4) ml./min.

normal animals, falling from a control value of 96 to 51 mm Hg (S.E. of diff. ± 4·2; $P < 0·01$) following inhalation of CO, whilst the corresponding figures in the normal group were respectively 88 and 70 mm Hg (S.E. of diff. ± 3·1; $P = 0·01$). The heart rate fell gradually from its initially high resting value (Korner, 1964) of 325 beats/min to 300 beats/min (S.E. of

diff. ± 4·6 beats/min; $P = 0{\cdot}01$), the changes in heart rate lagging behind those in blood pressure (Fig. 8).

During inhalation of 0·1 % CO there was also a marked fall in arterial pressure and TPR. The cardiac output was maintained at its elevated resting level, and there was a small increase in right atrial pressure, but no significant change in heart rate (Fig. 8).

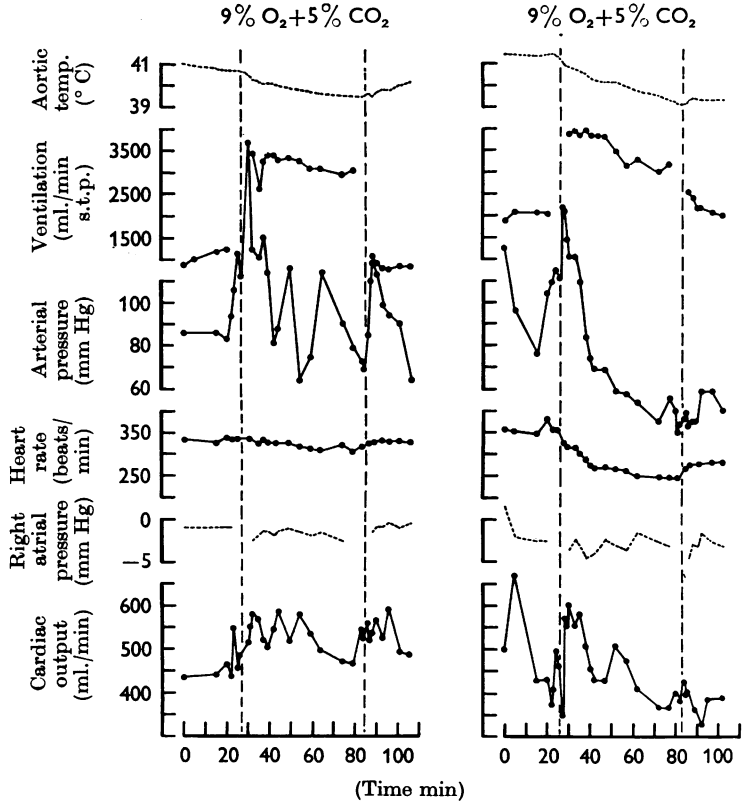

Fig. 9. *Left.* Results from one experiment in a 'denervated' rabbit during inhalation of 9 % O_2 + 5 % CO_2. A similar response pattern was observed in two other animals (see text). *Right.* Results from another experiment in a 'denervated' rabbit during inhalation of 9 % O_2 + 5 % CO_2. Further description in text.

The recovery from the effects of inhalation of CO was relatively slow, as was the case in the group of normal animals (cf. Figs. 5 and 8). However the effects of inhalation of CO mixtures were closely similar to the findings with low O_2 in the 'denervated' animals.

Interaction of effects of hypercapnia with those of low O_2 mixtures. In three 'denervated' rabbits the ventilation increased to 180 ± 15 (S.E. of mean) % of control after breathing 21 % O_2 + 5 % CO_2, the response

equalling that of normal animals. Circulatory changes were slight and not significant, apart from a constant initial rise of blood pressure by 19 ± 8 (S.E. of mean) mm Hg.

Inhalation of 9% O_2 + 5% CO_2 resulted in an increase in ventilation to 244 ± 26 (S.E. of mean) % of control, in four 'denervated' rabbits owing to a rise in P_{CO_2} to 40 mm Hg (range 32–48 mm Hg). This was well sustained in three of the animals (e.g. Fig. 9, left panel) suggesting absence of central respiratory depression due to hypoxia (mean P_{O_2} 38 mm Hg; range 27–48 mm Hg). In these animals, the blood pressure declined gradually after an initial rise, in a series of waves which were synchronous with smaller fluctuations in cardiac output (Fig. 9, left panel). There were no significant changes in heart rate and no evidence of potentiation of the circulatory effects of reduced P_{O_2} by an increase in P_{CO_2} of the type seen in normal animals.

In one 'denervated' rabbit, however, the response observed during inhalation of 9% O_2 + 5% CO_2 was strongly suggestive of the gradual development of central depression of the respiratory and vasomotor centres (Fig. 9, right panel). Inhalation of the gas mixture resulted in an initial rise of ventilation, blood pressure and cardiac output, but this was followed by a parallel decline in these variables as well as the heart rate, and there was also an exceptionally large reduction in aortic blood temperature.

DISCUSSION

Role of the arterial chemoreceptors

In the unanaesthetized rabbit reduction in arterial P_{O_2} to about 30 mm Hg results in bradycardia, reduction in cardiac output with rise of blood pressure and TPR, these changes being maximal during the early phase of hypoxia. The present experiments indicate that the above effects resulted from stimulation of the arterial chemoreceptors, since they were abolished following section of the carotid and aortic nerves and were not observed during inhalation of CO mixtures. The magnitude of the effects was increased in normal (but not 'denervated') rabbits by simultaneous elevation of arterial P_{CO_2} and reduction in P_{O_2}, suggesting interaction at the receptor site (Eyzaguirre & Lewin, 1961; Neil & Joels, 1963). Bradycardia and reduction in cardiac output occur most readily in rabbits with an inadequate respiratory response to inhalation of low O_2 (e.g. Fig. 4; Korner & Edwards, 1960*a*, *b*) and are not therefore a secondary consequence of hyperventilation. The bradycardia is probably not the result of stimulation of baroreceptors by the rise in blood pressure, since it can occur without such changes (e.g. Fig. 6). However, under normal conditions the

rise in blood pressure may potentiate the chemoreceptor effects on the heart rate owing to baroreceptor stimulation. The large reduction in aortic blood temperature did not appear to be a major direct factor in the reduction of heart rate and cardiac output, since a fall in aortic blood temperature induced in 'denervated' animals by hyperventilation was not usually (Fig. 9, left panel) accompanied by bradycardia.

The circulatory effects of strong chemoreceptor stimulation in the conscious rabbit are thus identical with the effects of hypoxic stimulation of the isolated chemoreceptors in dogs and cats with controlled ventilation (Bernthal *et al.* 1951; Daly & Scott, 1958, 1962, 1963*a*, *b*; Downing *et al.* 1962; Downing & Siegel, 1963; MacLeod & Scott, 1964), and previous experiments have demonstrated that the efferent pathways in some of the effects, such as bradycardia, are also similar in the rabbit to those of other species (Korner & Edwards, 1960*a*).

The present experiments demonstrate a grading of circulatory effects with increasing reduction in arterial P_{O_2}. With reduction in the latter to about 50 mm Hg the circulatory effects are very small but the well-known respiratory effects of chemoreceptor excitation are apparent (Heymans & Neil, 1958). Reduction in P_{O_2} to about 35 mm Hg results in tachycardia and increased cardiac output which is probably not of chemoreceptor origin (see below), but comparison of the 'steady state' effects of low O_2 and of CO-containing mixtures suggests that the chemoreceptors play an important part in the maintenance of the arterial pressure during moderate arterial hypoxia. With additional reduction in P_{O_2} to about 30 mm Hg bradycardia and transient reduction in cardiac output become manifest. Further reduction in P_{O_2} results in increasing bradycardia and sustained reduction in cardiac output (e.g. Fig. 4; Korner& Edwards 1960*b*) probably owing to greater excitation of the chemoreceptors.

There was no evidence in the present experiments that inhalation of CO-containing mixtures resulted in stimulation of the arterial chemoreceptors. This would be expected from the perfusion studies of Duke *et al.* (1952) and of Joels & Neil (1961), and the demonstration of excitation of chemoreceptors only at much higher P_{CO} levels than employed in the present experiments (Joels & Neil, 1962). The fall in blood pressure following prolonged inhalation of CO-containing mixtures might, however, be expected to stimulate chemoreceptors by analogy with the effects of carotid occlusion, or of haemorrhage (Landgren & Neil, 1951*a*, *b*). This did not seem to have occurred, in view of the absence of an increase in ventilation with a respiratory centre normally responsive to CO_2 (Fig. 6).

Role of arterial baroreceptors

A comparison of the effects of CO in the normal rabbit with those in the 'denervated' animal permits assessment of the role of the baroreceptor reflexes in systemic hypoxia in view of the absence of chemoreceptor excitation. The present experiments suggest that baroreceptor reflexes can account for the circulatory effects of inhalation of CO mixtures.

In the normal animal with intact baroreceptors the arterial pressure was reduced and the cardiac output increased, suggestive of some peripheral vasodilatation owing to tissue hypoxia (Korner, 1959). The fall in blood pressure would reduce the normal discharge from the arterial baroreceptors (Heymans & Neil, 1958), with resulting increase in sympathetic efferent discharge. This would result in a reflex increase in heart rate and myocardial contractility (Sarnoff, Gilmore, Brockman, Mitchell & Linden, 1960; Downing & Siegel, 1963) and arteriolar and venomotor tone (Heymans & Neil, 1958; Bartelstone, 1960; Ross, Frahm & Braunwald, 1961). In the rabbit and dog the increase of 10–20% in cardiac output, blood pressure and heart rate observed after section of the carotid sinus and aortic nerves (Bing, Thomas & Waples, 1945; Korner, 1965) probably represents the maximum reflex increase in these variables which can be mediated through the arterial baroreceptors in the presence of a normal tissue P_{O_2}.

Inhalation of CO-containing mixtures in the 'denervated' animal resulted in a large fall in blood pressure, but despite this the cardiac output and right atrial pressure were maintained or increased further, suggesting massive peripheral dilatation analogous to the haemodynamic pattern of an arteriovenous shunt (Cohen, Edholm, Howarth, McMichael & Sharpey-Schafer, 1948; Epsten, Shadle, Ferguson & McDowell, 1953; Schreiner, Freinkel, Athens & Stow, 1953). The hypotension observed during inhalation of CO mixtures differs from that resulting from administration of spinal anaesthetics or ganglion-blocking agents in man, the dog (Sancetta, Lynn, Simeone & Scott, 1952; Sancetta, 1955; Crumpton, Rowe, O'Brien & Murphy, 1954; Ross *et al.* 1961) and the rabbit (Korner, unpublished observations) where there is also reduction in cardiac output probably owing to more diffuse interruption of the efferent pathways to the capacitance vessels as well as to the resistance vessels. In the 'denervated' animal the findings are consistent with massive dilatation of predominantly resistance vessels, so that the initially high efferent sympathetic discharge to the heart and capacitance vessels could maintain the cardiac output or even allow it to increase with greater degree of arteriolar dilatation. The finding in the 'denervated' animal of greater increase in cardiac output when inhaling 0·2% CO than with 0·1% CO, suggests that hypoxia of

local tissue determines the degree of arteriolar dilatation. In the normal animal the degree of local dilatation during the inhalation of CO would be limited by a reflex increase in sympathetic discharge to the resistance vessels whilst at the same time the increased sympathetic discharge to veins and heart would contribute to the increase in cardiac output.

Whilst the baroreceptor reflexes can account qualitatively for the effects observed during inhalation of CO-containing mixtures in the present experiments, the question arises whether other reflexes must be invoked to account quantitatively for the findings. Denervation abolished the tachycardia observed during inhalation of CO-containing mixtures. However, the final heart rate was as high or higher in 'denervated' as in normal animals in view of the elevated resting value of the former, as was also the case with the cardiac output values. The heart rate or cardiac output of the 'denervated' animal were not maximal (Isbister, Korner & Mok, unpublished observations) so that an increase in these variables from other reflexogenic zones would have been possible. The results thus suggest that the baroreceptor reflexes can account for the circulatory effects of carbon monoxide without having to invoke other reflexes.

The effects of inhalation of mixtures with low concentrations of O_2 in the 'denervated' animals were similar to those produced by CO-containing mixtures indicating an essentially similar mode of action after section of afferents from both the chemoreceptors and baroreceptors. However, in the normal animal maintenance of the arterial pressure was much more efficient with low O_2 than with CO-containing mixtures, owing to the activity of the chemoreceptors. Under these circumstances no withdrawal of tonic baroreceptor impulses is possible, and the tachycardia and increased cardiac output observed after moderate hypoxia (9 % O_2) cannot be due to baroreceptor reflexes. A different mode of circulatory control is also suggested by quantitative differences in the effects resulting from inhalation of 9 % O_2 and 0·1 % CO, since, for example, a consistently greater tachycardia was observed with the former gas. It is possible that hypocapnia and stimulation of pulmonary afferents by hyperventilation which have been shown to produce tachycardia in the dog (Daly & Scott, 1958, 1963*a*, *b*; Daly & Hazzledine, 1963) may account for the tachycardia and increased cardiac output which follow moderate reduction in arterial P_{O_2}. Hyperventilation alone does not seem fully to account for these changes in the rabbit since no tachycardia resulted in 'denervated' animals hyperventilating in the course of hypercapnia. In intact man McGregor, Donevan & Anderson (1962) have demonstrated a greater increase in cardiac output and heart rate during hyperventilation in the presence of hypocapnia, and it is possible that both factors are necessary to elicit tachycardia, etc., in the rabbit during moderate arterial hypoxia.

Relation of the circulatory response to hypoxia of the rabbit to that of other species

Marked qualitative differences to inhalation of low O_2 mixtures have frequently been reported in the circulatory response of different species. The present experiments suggest a possible explanation of some of these species differences, since at different arterial oxygen tensions the circulatory response of the rabbit may simulate each of the 'species' responses previously reported. Thus with moderate reduction of arterial P_{O_2} to 35–40 mm Hg circulatory chemoreceptor effects other than on blood pressure were not in evidence, and the circulatory findings in the rabbit resembled those observed with similar reduction in P_{O_2} in man and the conscious dog (Harrison & Blalock, 1927; Doyle, Wilson & Warren, 1952; Nahas, Visscher, Mather, Haddy & Warner, 1954). With more severe reduction in arterial P_{O_2} the bradycardia and associated chemoreceptor effects resemble the circulatory effects of severe arterial hypoxia in diving animals (Irving, Scholander & Grinnell, 1941; Feigl & Folkow, 1963; Anderson, 1963; Scholander, 1964).

The rabbit, owing to its rapid shallow respiration, appears more limited than other species in its ability to increase alveolar ventilation, when exposed to mixtures with low O_2 concentrations (Dripps & Comroe, 1947; Rahn & Otis, 1947; Korner, 1959), so that greater reduction in alveolar P_{O_2} would result with consequently greater stimulation of the arterial chemoreceptors. In man and the dog reduction in arterial P_{O_2} below 30 mmHg is usually prevented by the large increase in ventilation at any given inspired O_2 concentration. However, under conditions when there is rapid reduction in arterial P_{O_2} and rise in P_{CO_2} with no ventilatory effort such as in underwater diving, bradycardia has been observed even in man (Olsen, Fanestil & Scholander, 1962), and also during severe hypoxia in the intact dog (Cross, Rieben, Barron & Salisbury, 1963), and it seems probable that these effects are also mediated by chemoreceptor reflexes.

By contrast, the circulatory and respiratory effects of inhalation of CO-containing mixtures were similar in the rabbit to those of other species (Asmussen & Chiodi, 1941; Chiodi, Dill, Consolazio & Horvath, 1941) which suggests that the species differences in response to low concentrations of O_2 are a consequence of inadequate ventilatory effort, and do not reflect an intrinsically greater susceptibility to hypoxia at the tissue level.

SUMMARY

1. The circulatory response of the conscious rabbit has been examined in normal animals and in animals with chronic section of carotid and aortic nerves during inhalation of low O_2 mixtures (arterial hypoxia) and when

breathing CO mixtures (tissue hypoxia), and the role of the arterial chemoreceptor and baroreceptor reflexes has been assessed.

2. In arterial hypoxia reduction in arterial P_{O_2} to 35–40 mm Hg resulted in a transient increase in cardiac output, tachycardia and maintenance of the arterial pressure. The chemoreceptor reflexes are responsible for the ventilatory response and contribute towards the maintenance of blood pressure.

3. Further reduction in arterial P_{O_2} to about 30 mm Hg results in bradycardia, transient reduction in cardiac output and a rise in blood pressure. These effects are of chemoreceptor origin. They are accentuated by simultaneous elevation of P_{CO_2} in normal but not in de-afferented rabbits.

4. There were no signs of chemoreceptor excitation in tissue hypoxia produced by inhaling CO in air. The circulatory response consisted of an increase in cardiac output, slight tachycardia and a fall in blood pressure. Baroreceptor reflexes limited the fall in arterial pressure and contributed to an increase in cardiac output in this type of hypoxia.

5. The circulatory responses to low O_2 in the normal rabbit simulate the varying responses of other species. Each species response appears related to the degree of reduction in arterial P_{O_2} and consequent degree of chemoreceptor stimulation, and not in intrinsic susceptibility to hypoxia since the responses to CO are all closely similar.

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REFERENCES

ANDERSON, H. T. (1963). Factors determining the circulatory adjustments to diving. II. Asphyxia. *Acta physiol. scand.* **58**, 263–278.

ASMUSSEN, E. & CHIODI, H. (1941). Effect of hypoxemia on ventilation and circulation in man. *Amer. J. Physiol.* **132**, 426–436.

BARTELSTONE, H. J. (1960). Role of the veins in venous return. *Circulation Res.* **8**, 1059–1076.

BERNTHAL, T. G., GREENE, W. JR. & REVZIN, A. M. (1951). Role of the carotid chemoreceptors in hypoxic cardiac acceleration. *Proc. Soc. exp. Biol., N.Y.*, **76**, 121–124.

BING, R. J., THOMAS, C. B. & WAPLES, E. C. (1945). The circulation in experimental neurogenic hypertension. *J. clin. Invest.* **24**, 513–421.

CHIODI, H., DILL, D. B., CONSOLAZIO, F. & HORVATH, S. M. (1941). Respiratory and circulatory responses to acute carbon monoxide poisoning. *Amer. J. Physiol.* **134**, 683–693.

COCHRAN, W. G. & COX, G. M. (1953). *Experimental Designs*. New York: Wiley.

COHEN, S. M., EDHOLM, O. G., HOWARTH, S., MCMICHAEL, J. & SHARPEY-SCHAFER, E. P. (1948). Cardiac output and peripheral blood flow in arterio-venous aneurysm. *Clin. Sci.* **7**, 35–47.

CROSS, C. E., RIEBEN, P. A., BARRON, C. I. & SALISBURY, P. F. (1963). Effects of arterial hypoxia on the heart and circulation: an integrative study. *Amer. J. Physiol.* **205**, 963–970.

CRUMPTON, C. W., ROWE, C. G., O'BRIEN, G. & MURPHY, Q. R. (1954). The effect of hexamethonium bromide upon coronary flow, cardiac work and cardiac efficiency in normotensive and renal hypertensive dogs. *Circulation Res.* **2**, 79–83.

DALY, M. DE B. & HAZZLEDINE, J. L. (1963). The effects of artificially induced hyperventilation on the primary cardiac reflex response to stimulation of the carotid bodies in the dog. *J. Physiol.* **168**, 872–889.

DALY, M. DE B. & SCOTT, M. J. (1958). The effects of stimulation of the carotid body chemoreceptors on the heart rate in the dog. *J. Physiol.* **144**, 148–166.

DALY, M. DE B. & SCOTT, M. J. (1962). An analysis of the primary reflex effects of stimulation of the carotid body chemoreceptors in the dog. *J. Physiol.* **162**, 555–573.

DALY, M. DE B. & SCOTT, M. J. (1963*a*). The cardiovascular responses to stimulation of the carotid body chemoreceptors in the dog. *J. Physiol.* **165**, 179–197.

DALY, M. DE B. & SCOTT, M. J. (1963*b*). The effects of changes in respiration on the cardiovascular responses to stimulation of the carotid body chemoreceptors. In *The Regulation of Human Respiration*, John Scott Haldane Centenary Volume, ed. CUNNINGHAM, D. J. C. & LLOYD, B. B., pp. 149–162. Oxford: Blackwell.

DAVENPORT, H. W., BREWER, G., CHAMBERS, A. & GOLDSCHMIDT, S. (1947). The respiratory response to anoxaemia of unanaesthetized dogs with chronically denervated aortic and carotid chemoreceptors and their causes. *Amer. J. Physiol.* **148**, 406–416.

DOWNING, S. E., REMENSNYDER, J. P. & MITCHELL, J. H. (1962). Cardiovascular responses to hypoxic stimulation of the carotid bodies. *Circulation Res.* **10**, 676–685.

DOWNING, S. E. & SIEGEL, J. H. (1963). Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart. *Amer. J. Physiol.* **204**, 471–479.

DOYLE, J. T., WILSON, J. S. & WARREN, J. V. (1952). Pulmonary vascular responses to short term hypoxia in human subjects. *Circulation*, **5**, 263–270.

DRABKIN, D. L. & AUSTIN, J. H. (1935). Spectrophotometric studies. II. Preparations from washed blood cells: nitric oxide hemoglobin and sulfhemoglobin. *J. biol. Chem.* **112**, 51–65.

DRIPPS, R. D. & COMROE, J. H., JR. (1947). Effect of inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) or normal individuals. *Amer. J. Physiol.* **149**, 227–291.

DUKE, H. N., GREEN, J. H. & NEIL, E. (1952). Carotid chemoreceptor activity during inhalation of carbon monoxide mixtures. *J. Physiol.* **118**, 520–527.

EDWARDS, A. W. T., KORNER, P. I. & THORBURN, G. D. (1959). The cardiac output of the unanaesthetized rabbit, and the effects of preliminary anaesthesia, environmental temperature and carotid occlusion. *Quart. J. exp. Physiol.* **44**, 309–311.

EPSTEN, F. H., SHADLE, O. W., FERGUSON, T. B. & MCDOWELL, M. E. (1953). Cardiac output and intracardiac pressure in patients with arteriovenous fistulas. *J. clin. Invest.* **32**, 543–547.

EYZAGUIRRE, C. & LEWIN, J. (1961). Chemoreceptor activity of the carotid body of the cat. *J. Physiol.* **159**, 222–237.

FEGLER, G. (1954). Measurement of cardiac output in anaesthetized animals by a thermodilution method. *Quart. J. exp. Physiol.* **39**, 153–164.

FEIGL, E. & FOLKOW, B. (1963). Cardiovascular responses in 'diving' and during brain stimulation in ducks. *Acta physiol. scand.* **57**, 99–110.

HALDANE, J. S. & PRIESTLEY, J. G. (1935). *Respiration*. Oxford: Clarendon Press.

HARRISON, T. R. & BLALOCK, A. (1927). Effects of severe anoxaemia of short duration on cardiac output of morphinized dogs and trained unnarcotized dogs. *Amer. J. Physiol.* **80**, 169–178.

HEYMANS, C. & NEIL, E. (1948). *Reflexogenic Areas of the Cardiovascular System*. London: Churchill.

HILL, R. (1936). Oxygen dissociation curve of muscle haemoglobin. *Proc. Roy. Soc.* B, **120**, 472–495.

IRVING, L., SCHOLANDER, P. F. & GRINNELL, S. W. (1941). Significance of the heart rate to the diving ability of seals. *J. cell. comp. Physiol.* **18**, 283–297.

JOELS, N. & NEIL, E. (1961). Carotid chemoreceptor impulse activity during inhalation of carbon monoxide mixtures. *J. Physiol.* **156**, 5*P*.

JOELS, N. & NEIL, E. (1962). The actions of high tensions of carbon monoxide on the carotid chemoreceptors. *Arch. int. Pharmacodyn.* **139**, 528–534.

KORNER, P. I. (1959). Circulatory adaptations in hypoxia. *Physiol. Rev.* **39**, 687–730.

KORNER, P. I. (1963). Effects of low oxygen and of carbon monoxide on the renal circulation in unanaesthetized rabbits. *Circulation Res.* **12**, 361–374.

KORNER, P. I. (1965). The effect of section of the carotid sinus and aortic nerves on the cardiac output of the rabbit. *J. Physiol.* **180**, 266–278.

KORNER, P. I. & DARIAN-SMITH, I. (1954). Cardiac output in normal unanaesthetized and anaesthetized rabbits. *Aust. J. exp. Biol.* **32**, 499–510.

KORNER, P. I. & EDWARDS, A. W. T. (1960*a*). The immediate effects of acute hypoxia on the heart rate, arterial pressure, cardiac output and ventilation of the unanaesthetized rabbit. *Quart. J. exp. Physiol.* **45**, 113–122.

KORNER, P. I. & EDWARDS, A. W. T. (1960*b*). The cardiac output during the steady-state in oxygen lack in the unanaesthetized rabbit and its relation to the early circulatory response. *Quart. J. exp. Physiol.* **45**, 129–141.

KORNER, P. I. & EDWARDS, A. W. T. (1960*c*). The effect of varying the inspired oxygen and carbon dioxide pressures on the cardiac output of the unanaesthetized rabbit. *Quart. J. exp. Physiol.* **45**, 123–128.

LANDGREN, S. & NEIL, E. (1951*a*). The contribution of carotid chemoreceptor mechanisms to the rise of blood pressure caused by carotid occlusion. *Acta physiol. scand.* **23**, 152–157.

LANDGREN, S. & NEIL, E. (1951*b*). Chemoreceptor activity following haemorrhage. *Acta physiol. scand.* **23**, 158–167.

MACLEOD, R. D. M. & SCOTT, M. J. (1964). The heart rate responses to carotid body chemoreceptor stimulation in the cat. *J. Physiol.* **175**, 193–202.

MCGREGOR, M., DONEVAN, R. E. & ANDERSON, N. M. (1962). Influence of carbon dioxide and hyperventilation on cardiac output in man. *J. appl. Physiol.* **17**, 933–937.

MATHER, K. (1949). *Statistical Analysis in Biology.* London: Methuen.

NAHAS, G. G., VISSCHER, M. B., MATHER, G. W., HADDY, F. J. & WARNER, H. R. (1954). Influence of hypoxia on pulmonary circulation of non-narcotized dogs. *J. appl. Physiol.* **6**, 467–476.

NEIL, E. & JOELS, N. (1963). The carotid glomus sensory mechanisms. In *The Regulation of Human Respiration*, John Scott Haldane Centenary Volume, ed. CUNNINGHAM, D. J. C. & LLOYD, B. B., pp. 163–171. Oxford: Blackwell.

OLSEN, C. R., FANESTIL, D. D. & SCHOLANDER, P. F. (1962). Some effects of breath holding and apnoeic underwater diving on cardiac rhythm in man. *J. appl. Physiol.* **17**, 461–466.

RAHN, H. & OTIS, A. B. (1957). Alveolar air during simulated flights to high altitudes. *Amer. J. Physiol.* **150**, 202–221.

ROSENTHAL, T. B. (1948). The effect of temperature on the pH of blood and plasma *in vitro*. *J. biol. Chem.* **173**, 25–30.

ROSS, J., JR., FRAHM, C. J. & BRAUNWALD, E. (1961). Influence of the carotid baroreceptors and of vasoactive drugs on systemic vascular volume and venous distensibility. *Circulation Res.* **9**, 75–82.

SANCETTA, S. M. (1955). Acute haemodynamic effects of hexamethonium (C6) in patients with emphysematous pulmonary hypertension. *Amer. Heart J.* **49**, 501–516.

SANCETTA, S. M., LYNN, R. B., SIMEONE, F. A. & SCOTT, R. W. (1952). Changes in cardiac output, brachial arterial pressure, peripheral and pulmonary oxygen contents and peripheral blood flows induced by spinal anaesthesia in humans not undergoing surgery. *Circulation*, **6**, 559–571.

SARNOFF, S. J., GILMORE, J. P., BROCKMAN, S. K., MITCHELL, J. H. & LINDEN, R. J. (1960). Regulation of ventricular contraction by the carotid sinus; its effect on atrial and ventricular dynamics. *Circulation Res.* **8**, 1123–1136.

SCHOLANDER, P. F. (1964). Animals in aquatic environments: diving mammals and birds. In *Handbook of Physiology. Section 4: Adaptation to the Environment*, ed. DILL, D. B., ADOLPH, E. F. & WILBER, C. G., pp. 729–740 Washington, C. D.: American Physiological Society.

SCHREINER, G. E., FREINKEL, N., ATHENS, J. W. & STOW, W. (1953). Cardiac output, central volume and dye injection curves in traumatic arteriovenous fistula in man. *Circulation*, **7**, 718–723.

SEVERINGHAUS, J. W. (1958). Oxyhaemoglobin dissociation curve correction for temperature and pH variation in human blood. *J. appl. Physiol.* **12**, 485–486.

SEVERINGHAUS, J. W., STUPFEL, M. & BRADLEY, A. F. (1956*a*). Accuracy of blood pH and P_{CO_2} determinations. *J. appl. Physiol.* **9**, 189–196.

SEVERINGHAUS, J. W., STUPFEL, M. & BRADLEY, A. F. (1956*b*). Variations of serum carbonic acid pK′ with pH and temperature. *J. appl. Physiol.* **9**, 197–200.

STOKES, G. S. & KORNER, P. I. (1964). Effect of posthaemorrhagic anaemia on the renal circulation of the unanaesthetized rabbit. *Circulation Res.* **14**, 414–425.

VAN SLYKE, D. D. & NEILL, J. M. (1924). The determination of gases in blood and other solutions by vacuum extraction and manometric measurements. *J. biol. Chem.* **61**, 523–573.

VAN SLYKE, D. D. & SENDROY, J., JR. (1928). Line charts for graphic calculations by the Henderson–Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. *J. biol. Chem.* **79**, 781–798.